UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,873	11/28/2005	Nikolai Soren Kirkby	P68228US1	7765

136 7590 08/03/2009

JACOBSON HOLMAN PLLC
400 SEVENTH STREET N.W.
SUITE 600
WASHINGTON, DC 20004

EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
08/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,873	KIRKBY ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-18,20,21,23,25-27 and 29-61* is/are pending in the application.

4a) Of the above claim(s) *11,12,14,15,29-31 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10,13,16-18,20,21,23,25-27,32-34 and 38-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on April 1, 2009 is acknowledged. Claims 1, 2, 4-18, 20, 21, 23, 25-27, 29-37 and 38-61 are pending. Claims 1, 4, 9-11, 13, 14, 16, 17, 20, 21, 23, 25, 26, 33 and 35-37 have been amended. Claims 11, 12, 14, 15, 29-31 and 35-37 have been previously withdrawn from further consideration as being drawn to non-elected inventions. Claims 19, 22 and 24 have been canceled. Claims 38-61 have been added. Claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 32-34 and 38-61 are currently under examination.

Rejections Withdrawn

Claim Rejections - 35 USC § 112

2. In view of Applicant's amendments, arguments and cancellation of claim 24, the rejection of claims 1, 2, 4-10, 13, 16-27 and 32-34 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention by the use of the terms "genetic determinant", "electrostatic interaction", "hydrophobic interaction", "contacting group", "enhancer", by the use of the phrase "immunological response may act upon subsequent exposure" and "immunogen and/or immunogen delivery system is separated from each other" is withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. The rejection of claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32, 34, 38-43, 46, 47, 49-55 and 57-61 under 35 U.S.C. 102(b) as being anticipated by Foldvari et al. (WO 99/11247) as previously rejected over claims 1, 2, 4, 5, 9, 10, 13, 16-18, 20, 21, 23, 25-27, 32 and 34 is maintained for the reasons set forth in the previous office action. The cancellation of claims 19, 22 and 24 renders the rejection of said claims moot.

Applicant argues that:

1) Claim 1 requires that the construct comprise a cationic sterol. Foldvari does not disclose or suggest cationic sterols.

2) Foldvari discloses at page 10, line 16 that the size of the residue is 0.1 to 100μm. They are thus, at a minimum 100 nm.

3) Claim 58 require that the complex is in the form of microparticles with a rigid structure and claim 59 that the structure is cage like.

4) There is no reference to vapor or gas transmission, or occlusion thereof, any where in the Foldvari disclosure.

5) Foldvari does not clearly disclose an occlusion (limited water vapor permeability) vehicle as required by claim 1.

6) Foldvari does not specifically disclose nucleic acids which are chosen because they encode an immunogenic protein.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system; wherein the immunogen delivery system is a complex comprising: i) at least one cationic sterol ii) at least one saponin, wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid, wherein said saponin is capable of forming a complex with said at least one cationic.

With regard to Point 1, Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol and cholestane (see page 8, lines 21-22), absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol.

With regard to Point 2, while Foldvari discloses that the size of the residue is between 0.1 to 100μm, which is at a minimum 100 nm. The Examiner appreciates Applicant's point, but notes that all of the pending claims do not recite a size limitation. Thus the argument is moot with regard to those claims. With regard to claim 57, Foldvari meets the limitation of at least 5nm.

With regard to Point 3, the limitation that the complex is in the form of microparticles with a rigid structure and that the structure is cage like is not a limitation of the independent claim. Moreover, in view of the 112/2 rejection below, the complex of Foldvari is necessarily cage like in structure; and the complex of Foldvari is necessarily rigid in structure since the structure is formed due to self-organizing inherent properties of the saponin.

With regard to Point 4, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., vapor or gas transmission, or occlusion thereof) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to Point 5, contrary to Applicant's argument, the claims are drawn in part to an occlusion vehicle. Foldvari discloses the use of an occlusion vehicle. Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., limited water vapor permeability) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to Point 6, Foldari discloses the use of immunogens, including nucleic acids. Foldari further discloses that the composition of the present invention

includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. Absent evidence to the contrary, the nucleic acid of Foldari necessarily encodes an immunogen capable of eliciting a protective immune response against a pathogenic microorganism as well as a nucleic acid that is necessarily expressible by cells in an individual.

As previously presented, Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al. disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the lipid vesicles cross the membrane to contact and penetrate the skin for administration of the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not

limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens, *Helicobacter pylori* antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3 capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13). Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from

microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The rejection of claims 1, 2, 4-6, 9, 10, 13, 16-18, 20, 21, 23-27, 32-34, 38-43 and 46-61 under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) and British Pharmacopoeia 1993 (Surgical Materials, 1996; 1943-1944) as previously rejected over claims 1, 2, 4-6, 9, 10, 13, 16-27, 32-34 is maintained for the

reasons set forth in the previous office action. The cancellation of claims 19, 22 and 24 renders the rejection of said claims moot.

Applicant' argues that:

1) Claim 1 requires that the construct comprise a cationic sterol. Foldvari does not disclose or suggest cationic sterols.

2) The Posintro complex of 5 to 50nm is much smaller then the lipid vesicles of Foldvari, which is typically between 0.1 to 100μm.

3) Posintro is a chemical complex without a central compartment and the delivery effect on the immunogen is not related to any oil-in-water emulsion.

4) The adjuvant effect of the Posintro is based in the fact that it can form a complex in nano size with the immunogen/protein, which can permeate the skin and reach the target cells, in spite of the size of the complex, which is surprising.

5) There is no indication in Foldvari that the lipid vesicles can permeate the skin or cell membrane.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system; wherein the immunogen delivery system is a

complex comprising: i) at least one cationic sterol ii) at least one saponin, wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid, wherein said saponin is capable of forming a complex with said at least one cationic.

With regard to Point 1, Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol and cholestane (see page 8, lines 21-22), absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol.

With regard to Point 2, while Foldvari discloses that the size of the residue is between 0.1 to 100µm, which is at a minimum 100 nm. The Examiner appreciates Applicant's point, but notes that all of the pending claims do not recite a size limitation. Thus the argument is moot with regard to those claims. With regard to claim 57, Foldvari meets the limitation of at least 5nm.

With regard to Point 3, In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a chemical complex without a central compartment and the delivery effect on the immunogen is not related to any oil-in-water emulsion) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to Point 4, Applicant's assertion of unexpected results, Applicant has failed to provide evidence supporting said assertion. The MPEP states:

716.02(b) Burden on Applicant
BURDEN ON APPLICANT TO ESTABLISH RESULTS ARE UNEXPECTED

AND SIGNIFICANT
The evidence relied up should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants' brief that the claimed polymer had an unexpectedly increased impact strength "are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration."); Ex parte C, 27 USPQ2d 1492 (Bd. Pat. App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean plant, however there was no basis for judging the practical significance of data with regard to maturity date, flowering date, flower color, or height of the plant.). See also In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and In re Eli Lilly, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP § 716.02(c).
APPLICANTS HAVE BURDEN OF EXPLAINING PROFFERED DATA
"[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." Ex parte Ishizaka, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992).
DIRECT AND INDIRECT COMPARATIVE TESTS ARE PROBATIVE OF NONOBVIOUSNESS
Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See In re Blondel, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and In re Fouche, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a prima facie case of obviousness. The patentability of an intermediate may be established by unexpected properties of an end product "when one of ordinary skill in the art would reasonably ascribe to a claimed intermediate the contributing cause' for such an unexpectedly superior activity or property." In re Magerlein, 602 F.2d 366, 373, 202 USPQ 473, 479 (CCPA 1979). "In order to establish that the claimed intermediate is a contributing cause' of the unexpectedly superior activity or property of an end product, an applicant must identify the cause of the unexpectedly superior activity or property (compared to the prior art) in the end product and establish a nexus for that cause between the intermediate and the end product." Id. at 479.

Additionally, 716.01(c) Probative Value of Objective Evidence TO BE OF PROBATIVE VALUE, ANY OBJECTIVE EVIDENCE SHOULD BE SUPPORTED BY ACTUAL PROOF
Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that

unexpected results must be established by factual evidence." "[A]ppellants have not presented any experimental data showing that prior heat-shrinkable articles split. Due to the absence of tests comparing appellant's heat shrinkable articles with those of the closest prior art, we conclude that appellant's assertions of unexpected results constitute mere argument."). See also In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); Ex parte George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991).

ATTORNEY ARGUMENTS CANNOT TAKE THE PLACE OF EVIDENCE
The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

With regard to Point 5, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., lipid vesicles can permeate the skin or cell membrane) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As previously presented, Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al.

disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the lipid vesicles cross the membrane to contact and penetrate the skin for administration of the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens, *Helicobacter pylori* antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3 capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations

thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13). Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Foldvari et al. do not specifically disclose the use of a hydrocolloid adhesive or that one of the two compartments comprises a lyophilized pad comprising the immunogen and the other compartment comprises water or other appropriate solvent/diluent. Foldvari et al. do not specifically disclose that the cationic sterol is DC-cholesterol.

British Pharmacopoeia 1993 discloses wound dressings and medicated bandages, which include a semipermeable hydrocolloid dressing (see page 1943).

Foldvari et al. and British Pharmacopoeia 1993 disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was made to use the hydrocolloid dressing of British Pharmacopoeia 1993 because it is a sterile, self-adhesive, waterproof, multi-component structure that would be effective in delivering at least one immunogen to an individual. Moreover, it would have been obvious at the time the invention was made to use the hydrocolloid because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, it would have been obvious to modify the compartments disclosed in Foldvari et al. to have the first compartment comprise a lyophilized pad comprising the immunogen and a second compartment comprise water or other appropriate solvent/diluent to help with preservation of the immunogen, inhibit the action of microorganisms and enzymes that would normally spoil or degrade the substance, to increase the shelf life and to quickly and easily rehydrate or reconstitute.

Moreover, with regard to claim 48, it would have been obvious to use DC-cholesterol because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

It would have been expected, barring evidence to the contrary, that the hydrocolloid dressing would be effective for transdermal delivery of at least one immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

With regard to claim 56, limitations such as the size of a microparticle are being viewed as limitations of optimizing experimental parameters. By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

5. The rejection of claims 1, 2, 4, 5, 7-9, 10, 13, 16-27, 32-34, 38-43, 46, 47, 49-55 and 57-61 under 35 U.S.C. 103(a) as being unpatentable over Foldvari et al. (WO 99/11247) and Lee et al. (International Journal of Pharmaceutics, 2001; 221: 1-22) as previously rejected over claims 1, 2, 4, 5, 7-9, 10, 13, 16-27, 32-34 is maintained for the reasons set forth in the previous office action. The cancellation of claims 19, 22 and 24 renders the rejection of said claims moot

Applicant' argues that:

1) British Pharmacopeia fails to remedy the deficiencies of Foldvari as discussed in the context of anticipation (claim 1 requires that the construct comprise a cationic sterol. Foldvari does not disclose or suggest cationic sterols).

2) The Posintro complex of 5 to 50nm is much smaller then the lipid vesicles of Foldvari, which is typically between 0.1 to 100μm.

3) There is no indication in Foldvari that the lipid vesicles can permeate the skin or cell membrane.

Applicant's arguments have been considered and are deemed non-persuasive.

The rejected claims are drawn to a construct for transdermal delivery of at least one immunogen to an individual comprising:

a) said at least one immunogen, or at least one expressible nucleic acid encoding said immunogen;

b) an occlusion vehicle and

c) an immunogen delivery system; wherein the immunogen delivery system is a complex comprising: i) at least one cationic sterol ii) at least one saponin, wherein, if the construct comprises said nucleic acid, said cationic sterol or said saponin interacts electrostatically or hydrophobically with said nucleic acid, wherein said saponin is capable of forming a complex with said at least one cationic.

With regard to Point 1, Foldvari discloses sterols such as cholesterol, coprostanol, cholestanol and cholestane (see page 8, lines 21-22), absent evidence to the contrary, the sterol of Foldvari is necessarily a cationic sterol.

With regard to Point 2, while Foldvari discloses that the size of the residue is between 0.1 to 100μm, which is at a minimum 100 nm. The Examiner appreciates Applicant's point, but notes that all of the pending claims do not recite a size limitation.

Thus the argument is moot with regard to those claims. With regard to claim 57, Foldvari meets the limitation of at least 5nm.

With regard to Point 3, contrary to Applicant's argument, the claims are drawn in part to an occlusion vehicle. Foldvari discloses the use of an occlusion vehicle. Moreover, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., limited water vapor permeability) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As previously presented, Foldvari et al. disclose a biphasic lipid vesicle composition for transdermal administration. The transdermal device comprises a reservoir adapted to retain during storage and release in operation lipid vesicles containing an entrapped immunogen (see page 12, lines 18 and 19). The transdermal device includes a reservoir with a backing layer and membrane joined by an adhesive (see page 12, lines 22-25). Foldvari et al. disclose that the backing layer serves as a protective, impermeable covering to prevent loss of contents. Suitable backing materials include films for medical use (see page 12, lines 31-33). Foldvari et al. disclose that the device can be applied directly to the skin (see page 12, line 14). Foldvari et al. disclose that the reservoir includes lipid vesicles in suspension, and the lipid vesicles cross the membrane to contact and penetrate the skin for administration of

the entrapped immunogen (see page 14, lines 13-15). Also, Foldvari et al. disclose that the membrane is designed to be a rate controlling membrane (see page 14, line 24).

Foldvari et al. disclose that the composition of the present invention includes a suspension containing an entrapped immunogen effective to elicit an immune response, e.g., for purposes of immunization or vaccination. In general, a wide variety of immunogens are suitable for use in the present invention, they include but are not limited to influenza virus antigens *Bordetella pertussis* antigens (such as pertussis toxin, filamentous haemagglutinin, pertaetin), human papilloma virus (HPV) antigens, *Helicobacter pylori* antigens, rabies antigens, tick-borne encephalitis (TBE) antigens, meningoccal antigens (such as capsular polysaccharides of serogroup A, B, C, Y and W-135), tetanus antigens (such as tetanus toxoid), diphtheria antigens (such as diphtheria toxoid), pneumococcal antigens (such as *Streptococcus pneurnoniae* type 3 capsular polysaccharide), tuberculosis antigens, human immunodeficiency virus (HIV) antigens (such as GP-120, GP-160), cholera antigens (such as cholera toxin B subunit), 5 staphylococcal antigen (such as staphylococcal enterotoxin B), shigella antigens (such as shigella polysaccharides), vesicular stomatitis virus antigen (such as vesicular stomatitis virus glycoprotein), cytomegalovirus (CMV) antigens, hepatitis antigens (such as hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and G (HGV) virus antigens, respiratory syncytial virus (KSV) antigens, herpes simplex antigens, or combinations thereof(e.g.,10 combinations of diphtheria, pertussis and tetanus (DPT)), antigens against anthrax and *Yersinia pestis* (see page 6, lines 22-33 and page 7, lines 1-13).

Moreover, in addition to the vesicle-forming lipid component, the invention can include other lipid components capable of being incorporated into lipid bilayers, which for example can include sterols, saponin and Quil A (see page 8, lines 17-19 and 21; page 12, line 6). Foldvari et al. disclose that the adhesive layer that sticks to the skin is made from a pharmaceutically acceptable pressure sensitive adhesive (see page 13, lines 12-14). Foldvari et al. disclose that a wide variety of immunogens are suitable for use in the present invention, which include but are not limited to antigens derived from microorganisms, such as a virus, bacteria, parasite and/or fungus (see page 6, lines 27-33 and page 7, lines 1-20). Foldvari et al. discloses that the biphasic lipid vesicles of the invention include in the central core compartment of the lipid vesicle and in the aqueous space separating the lipid bilayers, an oil-in-water emulsion (see page 7, lines 23-25). Foldvari et al. disclose the use of enhancers such as monolauroyllysine or dipalmitoyllysine, an unsaturated fatty acid, such as oleic acid, a short chain fatty acid, such as lauric acid or methyl salicylate (see page 11, lines 15-19).

Foldvari et al. do not specifically disclose the use of a hydrogel adhesive, cross-linked or otherwise, nor do they disclose that one of the two compartments comprises a lyophilized pad comprising the immunogen and the other compartment comprises water or other appropriate solvent/diluent.

Lee et al. disclose that hydrogels have been widely used as a drug carrier (see page 10; section 3.5)

Foldvari et al. and Lee et al. disclose analogous inventions related to a product for transdermal delivery. It would have been obvious at the time the invention was

made to use a hydrogel because of its ease in manufacturing and self application (see Lee et al. Page 10). Moreover, it would have been obvious at the time the invention was made to use the cross-linked hydrogel because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Further, it would have been obvious to modify the compartments disclosed in Foldvari et al. to have the first compartment comprise a lyophilized pad comprising the immunogen and a second compartment comprise water or other appropriate solvent/diluent to help with preservation of the immunogen, inhibit the action of microorganisms and enzymes that would normally spoil or degrade the substance, to increase the shelf life and to quickly and easily rehydrate or reconstitute.

It would have been expected, barring evidence to the contrary, that the hydrogel would be effective for transdermal delivery of at least one immunogen. KSR forecloses the argument that a **specific** teaching, suggestion, or motivation is required to support a finding of obvious. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

By all comparative data the composition of the prior art and the instantly claimed composition absent evidence to the contrary are one in the same.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 23, 56, 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claim 23 to recite "an immunologically cross-reactive antigen...". This phrase does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Applicant does not point to a page to support said amendment.

Applicant has added claim 56 which recite "microparticles with an average diameter of *not more* than 50 nm". This phrase does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Applicant points to page 14, line 14 and page 40, lines 21-23 for support for said amendment, however, those pages are not relevant with regard to said limitation.

Applicant has added claims 58 and 59 which recite "...rigid microparticles (58)" and “case-like structures (59)”. This phrase does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in

the application, and none is apparent. Applicant points to page 29, line 28 and page 30 line 3 for support for said amendment, however, those pages are not relevant with regard to said limitation.

To overcome this rejection Applicant must specifically point out the support for this limitation or cancel the new matter from the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 4-10, 13, 16-18, 20, 21, 23, 25-27, 32-34 and 38-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 is rendered vague and indefinite by the use of the terms “case-like structure”. It is unclear what is meant by said term, as it is not explicitly defined in the specification. What constitutes a “case-like structure”? What core features/structures must be maintained? As written, it is impossible to determine the metes and bounds of the claimed invention.

Conclusion

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner,
Art Unit 1645

LJT
7/27/09